"variations and/or optimizations of the dosage regimen of compounds well known to be useful in HRT together sequentially or simultaneously are considered within the skill of the artisan." The rejection/allegation misses the point.

First, the alleged variations and/or optimizations necessary to achieve sequential or simultaneous administration are distinct from intermittent administration, which is one of the features of the present invention which none of the cited references teach or suggest.

Second, while it may be within the skill of one of ordinary skill in the art to optimize dosage regimens of a known compound, the intermittent administration of estrogen sulfamates is not merely an optimization procedure when the prior art only teaches the daily administration of the same. The intermittent administration of the compounds is an entirely new administration model. WO '216, as alleged, only teaches the daily administration of 10 micrograms per day of an estradiol, ethinyl estradiol, and estriol while also disclosing a generic formula which encompasses estriol-3-sulphamate. US '694 teaches the continuous administration of estrogen with norprogestrone. Based on the disclosure of the references, one of skill in the art would have understood that administration should be performed daily for the estrogen sulfamates as is taught for the other forms of the estrogen, and thus, would have optimized the amount per day of said compound to be administered to a patient even if the sulfamate form of the estrogen was chosen, for which no motivation exists over other disclosed species of the generic formula. No teaching or suggestion exists in the references that administration should be intermittently, for example, weekly, or even monthly. Thus, one of skill in the art would not have been motivated to try administering the compounds intermittently.

The specification teaches that natural estrogens are known to be quickly eliminated from the blood, even in cases where oral administration is given daily, and that an increase of the dose by no means is a mode for controlling the problem of strong fluctuations of the estrogen levels, i.e., fast elimination of the estrogens, from the blood. See specification on page 3 in its entirety and page 4, lines 1-4, and citations therein to Kuhnz et al. and Heithecker et al. The same is apparent from the Elger documents appearing on the Information Disclosure Statement filed on June 21, 2001. Especially see figures 9 and 10 from page 586 of the reference from Expert. Opin. Invest. Drugs showing that corresponding animal tests demonstrated that sulfamates released essentially all the estrogen after 24 hours. See also page 399 of

the reference from J. Steroid Biochem. Molec. Biol. showing a dose determining study where only daily administration of estrogen sulfamates and other forms of estrogen was attempted to evaluate the hepatic estrogenic activity of the hormones. One of skill in the art knowing that estrogens are quickly eliminated from the blood and that an increased dose does not overcome this problem would have not only have lacked the motivation to try administering the estrogens intermittently, but would have had a prejudice against doing so.

The specification also teaches that the administration of estradiol sulfamate to ovarioectomized rats, while leading to prolonged and higher blood levels of estradiol and estrone than an equimolar dose of estradiol, did not result in an extension of the estrogen actions, even at very high doses. However, surprisingly, the release of the noted hormones form the sulfamate prodrug proceeded much more slowly in humans than in rats. No such teaching or suggestion is found in the prior art. Additionally, applicants unexpectedly found that the period of estrogen release and hormone action could be affected by the level of the dose of the sulfamate prodrug of estrogen. Pharmacologically relevant blood levels were measured even after 4 weeks after a one-time administration. See specification on page 11, last 10 lines, and page 12, lines 1-5, the examples, and the figures. No such results could have been expected from the teachings of the prior art.

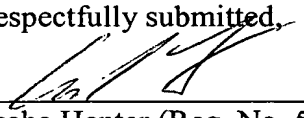
Applicants also found that uniform and well defined levels of natural estrogens can be built up in the blood by the administration of the sulfamate prodrug of the estrogens. See specification on page 13, third full paragraph. Applicants attach a figure submitted during the PCT proceeding which demonstrate this phenomena. The figure shows a simulation of the distribution of the biologically active main metabolite estrone in blood levels, shown in the accumulation of the estrone after the oral application of 2 mg estradiol sulfamate in weekly intervals in postmenstrual women. It is seen that maxima and minima of estrone in the blood levels increase up to the 4^{th} or 5^{th} application. This means, after the 4^{th} or 5^{th} application the relation between the maxima and minima is adjusted and is comparable with medicaments administered in 24 hour intervals. No such results could have been expected from the teachings of the prior art.

Based on these results, applicants found that, due to the slow release of the natural estrogens, in connection with a high oral bioavailability of the steroid portion of the administered estradiol sulfamate, administration can be conducted at larger

intervals, i.e., can be conducted intermittently. No teaching or suggestion in the prior art references to this effect can be found, which would supply the requisite motivation to one of skill in the art to administer the estrogen sulfamates intermittently. Thus, the intermittent administration of estrogen sulfamate is not obvious. Reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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